REMARKS

Applicant and applicant's attorney thank the Examiner for the courtesies extended during the telephone interview of 12 August 2008 and subsequent discussion with the undersigned. In furtherance of these discussions and in order to place the application in condition for allowance, applicant now proposes the above amendments to the independent claims. Other claims which depend therefrom are amended to conform with the proposed language of independent claims. The Examiner is requested to make the O'Brien reference (U.S. 4,904,605) and the Hochstrasser reference (U.S. 4,059,407) of record in this application. These and other references the Examiner considers relevant are now discussed to demonstrate allowability of all claims.

It is submitted that the claims now more fully distinguish over all combinations of the prior art. Claim 1 is exemplary, distinguished because it now requires that change in analyte concentration

"is determined based on capillary flow of each sample from a sample receiving region on one of the test devices to another region on the same test device and the response on each device is based on an amount of binding of an antigen and an antibody to form complexes."

None of the prior art, alone or in combination, suggests such a method for comparing a visually observable response induced in a first test device at a first time directly with a visually observable response induced in a second test device at a second time to provide information about a change in the level of analyte concentration between the two times. The **O'Brien** reference (U.S. 4,904,605) does not provide any motivation which would render the claim obvious. Applicant's method according to claim 1 is based on capillary flow to generate multiple sensitivity levels and the responses are based on binding of antigens with antibodies to form complexes. None of the disclosure in the O'Brien reference is consistent with this. Moreover, the O'Brien reference as best understood is only directed to quantitative testing which renders it unnecessary to compare results between different tests in order to determine characteristics such as total hardness (grains per gallon) or total chlorine in parts per million. See column 3, lines 4 - 44. Further, as noted at col. 3, lines 57 ff, O'Brien discloses a dipstick method which is inconsistent with the claimed method. Applicant's method requires flow from a sample receiving region on one of the test devices to another region on the same test device.

It is also submitted that the **Becket reference** (U.S. 5,710,372) fails to provide any disclosure which might (alone or in combination with other prior art) suggest obviousness of the claimed subject matter. The Becket reference , like O'Brien, does not at all relate to flow from a sample receiving region on one of the test devices to another region on the same test device. Furthermore, Becket as best understood is only directed to "measuring concentration of a constituent" (see abstract) and with a "visually unambiguous indication of concentration" (see col. 4, lines 5-9) such quantitative testing renders it unnecessary to compare results between different tests.

Claim 1 is also distinct and non-obvious over any combination of the foregoing with the **Toranto reference** (U.S. 2003/0175992) and/or the **Boehringer reference** (WO98/39657). As noted in the Second Appeal Brief, the devices of Toronto (analogous to the dipstick method of O'Brien) are each individually capable of providing desired information without requiring any comparison between assay tests. The Toranto reference only discloses a device responsive at one sensitivity level. This is true for all disclosed embodiments, including the embodiments having multiple collection sites as described in the last sentence of paragraph [0009] of the Toranto reference. Apparently, this is why it is satisfactory for the "preferred embodiments" among the multiple Toranto embodiments described in paragraph [0156] to provide an on/off readout if the alcohol concentration is above a certain threshold.

As described in the Summary of the Invention, the Boehringer reference discloses methods, devices and kits for **visually quantifying** the amount of analyte in a sample. FIGS 2 and 3 are illustrative of a single device which includes multiple test regions 16. In FIG 2, multiple separate matrices or regions each define a flow path emanating from a common sample zone. Barrier or threshold levels are set for each region to assess concentration of analyte when portions of the sample are applied among the multiple zones. See pp. 25 – 26 of the reference. In FIG 3, there is shown a "multi-flow path device" in which each flow path utilizes a different concentration of soluble antibody to facilitate creation of a different threshold response level for purposes of quantitation. See page 28. As stated at page 28, "soluble antibody concentrations and barrier zone break-through thresholds could be used to modulate the response ... of each flow path and facilitate quantitation." The text at pp 28-29 goes on to state that this is useful when concentration of analyte in a sample occurs over a wide dynamic range such that

> "at low analyte concentrations color will only appear on flow paths having low concentrations of soluble antibody ... [but] as analyte concentration increases, color will also appear on detection zones on flow paths having higher amounts of soluble antibody."

Based on these excerpts, it is accurate to characterize the Boehringer reference as concerning **quantitation of analyte concentration levels from a single source**, with portions of the source being concurrently provided along each of the several flow paths so as to identify and count a number of visual responses among the multiple flow paths. Accordingly, it is possible to visually assess relative concentration of analyte in the source by observing the number of colored lines appearing on the test units in a single device. To the extent the reference uses the term sample with regard to different receiving zones it is only in the context of providing portions of the same sample in different zones, e.g., portions of the source taken on the same occasion from a single source and applied concurrently along multiple flow paths to observe or count a number of lines or colored zones. The number of lines or zones can be correlated with analyte concentration in the sample based on a calibration methodology. See, also, p. 31, lines 1 – 12.

The Boehringer reference **only** addresses quantitation of analyte concentration relative to a single device such as shown in the figures, e.g., FIG 2. This reference does not at all disclose, imply or suggest any methodology relating to the change in an analyte concentration level over time, e.g., based on obtaining samples from the same source on different occasions. As an example, the above-discussed needs to monitor hCG levels for purposes of assessing health of a pregnancy are not at all contemplated by the Boehringer reference.

The **Hochstrasser reference** (U.S. 4,059,407) appears **less relevant** than the Boehringer reference. Hochstrasser discloses "immersing an instrument of the invention" (see col. 2, lines 51-57) and determining "presence and concentration of any chemical substance" (col. 3, lines 15-17) using "reagents for quantitative detection of the substance being analyzed ..." (col. 5, lines 1 - 3, see, also, lines 16-21) but does not at all relate to

"comparing a visually observable response induced in a first test device at a first time directly with a visually observable response induced in a second test device at a second time to provide information about a change in the level of analyte concentration between the two times."

Claims 10 and 20 are distinguishable for reasons similar to those presented above regarding claim 1 and more. For example, claim 10 now requires

providing first and second lateral flow test units each of the type which includes a receiving zone for fluid samples separated from two or more regions, each region responsive to analyte migrating from the receiving zone by capillary flow into the region, the two or more regions on each test unit defining multiple measurably distinguishable sensitivity levels each distinguishable sensitivity level indicative of a different amount of analyte in the source;

Claim 10 also requires:

a difference between visually observable responses induced in the first test device at the first time and induced in the second test device at the second time, each based on binding of an antigen and an antibody, provides information about a change in the level of analyte concentration present in the source between the two times.

It is submitted that *claim 25* remains distinct and non-obvious because it continues to require:

comparing a visually observable response induced in the first test device directly with a visually observable response induced in the second test device to provide information about a change in the level of analyte concentration without requiring determination of analyte concentration in the source on either occasion.

Furthermore, the method of claim 25 has been amended to further distinguish over the prior art by now requiring

providing multiple unitary test devices, each unitary test device including a plurality of regions, **each region being a responsive component in a ligand recognition system, based on capillary flow from a receiving zone**, to a different sensitivity level to indicate presence of the analyte in the source without being determinative of a numerical concentration of the analyte in the source …

Summary and Conclusion

In view of the above amendments and the distinctions described herein the claims each recite non-obvious subject matter. It would not be appropriate to combine any of the prior art to reject the claims because there is no combination that would result in the claimed combinations. While it may be permissible to reconstruct the prior art, any such efforts cannot be inconsistent

with the teachings in the prior art. It is only in hindsight recognition of the applicant's teachings that the O'Brien and Hochstrasser and Becket references might be considered. In each instance, these references do not at all relate to immunoassays, i.e., binding between an antigen and its homologous antibody. Nor do they require comparison of analyte levels on different occasions. This is because they all each relate to quantitative determinations of concentrations. There is no motivation or rationale to combine any of the foregoing with any other art of record to reject the claims as now presented.

For all of the above reasons allowance of the application is requested.

Respectfully submitted,

/Ferdinand M. Romano/

Ferdinand M. Romano
Registration No. 32,752
Beusse Wolter Sanks Mora & Maire, P.A.
390 N. Orange Avenue, Suite 2500
Orlando, FL 32801
(407) 926-7722

21 October 2008